An internal RJR document shows that the industry views nicotine's role as pharmacological and distinct from the smoke components that provide flavor:

> If nicotine is the sine qua non of tobacco products, and tobacco products are recognized as being attractive dosage forms of nicotine, then it is logical to design our product - and where possible our advertising - *around nicotine delivery rather than tar delivery or flavor.*[346]

Other industry documents further demonstrate that the industry understands that nicotine's role is primarily pharmacological and that any sensory role is secondary. A variety of industry documents shows that industry knows that "satisfaction" comes from inhalation of nicotine into the lungs and absorption into the bloodstream. *See* Jurisdictional Analysis, 60 FR 41773–41774. Inhalation is necessary only to provide systemic pharmacological effects; it would be unnecessary if nicotine's role were to provide sensory effects. The statements of tobacco industry scientists confirm that nicotine's pharmacological effects are the primary reason for tobacco use. A leading tobacco research director noted as early as 1972 that "[t]he primary incentive to cigarette smoking is the immediate salutary effect of inhaled smoke upon body function . . . . *the physiological effect serves as the primary incentive; all other incentives are secondary.*"[347] As recently as 1992, RJR researchers recognized that "smokers use cigarettes primarily as a 'tool' or 'resource' that provides them with needed psychological benefits (increased mental alertness; anxiety reduction, coping with stress)."[348]

---

[346] Teague CE, *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Feb. 2, 1973), at 3 (emphasis added). *See* AR (Vol. 531 Ref. 125).

[347] Dunn WL, Philip Morris Research Center, *Motives and Incentives in Cigarette Smoking* (1972), at 3-4 (emphasis added). *See* AR (Vol. 34 Ref. 582).

[348] Robinson JH, Pritchard WS, The role of nicotine in tobacco use, *Psychopharmacology* 1992; 108: 397-407 (emphasis added). *See* AR (Vol. 104 Ref. 945).

Literally dozens of such statements—made over decades by tobacco researchers and executives from virtually every major company—expose the industry's knowledge that consumers use tobacco products primarily for pharmacological effects. These statements are analyzed in depth in section II.C.2., below. By contrast, over this long period, there are virtually no tobacco company studies supporting the importance of the purported "sensory effects" of nicotine.

Second, the industry offers no persuasive data that nicotine contributes significantly to desirable flavor. FDA has reviewed all seven studies cited by the tobacco industry to demonstrate a significant "sensory" role for nicotine and finds them unpersuasive.

The industry cites a single abstract, based on research partially funded by RJR, to justify the claim that nicotine provides "trigeminal ('throat grab') stimulation that is enjoyed by smokers." The abstract describes a single study of trigeminal nerve manipulation in rats.[349] It is impossible to conclude from this study that nicotine stimulates the human trigeminal nerve in any manner significant to smokers.[350]

The industry cites a single paper to show that nicotine provides aroma "that is enjoyed by smokers." This research is based on recordings of the olfactory nerve in frogs.

---

[349] Silver WL, Walker DB, *Nasal trigeminal chemoreception: response to nicotine*, presented at the Ninth Annual Meeting of the Association for Chemoreceptor Sciences, Sarasota FL (1987). *See* AR (Vol. 535 Ref. 96, vol. III.M).

[350] The industry's "trigeminal nerve" theory seems to be based in part on an anatomic misunderstanding. The industry proposes that the sensation of "throat grab" is caused by nicotine stimulation "in the back of the throat (where trigeminal nerve endings are located)." In fact, sensation to the back of the throat (pharynx) in humans is provided by the glossopharyngeal nerve, not by the trigeminal nerve. *See* Williams PL, Warwick R, eds., *Gray's Anatomy*, 37th ed. (Philadelphia: WB Saunders, 1989), at 1112. *See* AR (Vol. 711 Ref. 8).

It is impossible to conclude from this study that nicotine creates an aroma of any significance to smokers.[351] Indeed, another study also cited by the industry concluded that reducing the olfactory stimulus of cigarettes had a minor effect on smoking behavior.[352]

RJR cites one article from 1952 and three recent studies to support the contention that the sensory aspects of nicotine consumption are more important to users than its pharmacological effects.

In a 1952 article cited by RJR for the proposition that nicotine plays an important role in the taste and flavor of cigarette smoke, there are no data on this subject.[353] The relevant statements are merely the authors' speculations. In fact, the authors speculated about the flavors of various types of tobacco leaves, not about the specific flavor of nicotine. Nor did the authors distinguish between flavor and pharmacological effects of nicotine; to the contrary, a portion of the article omitted by the comment states that "the smoker's desires are not satiated by" a low-nicotine leaf. This observation is consistent with the conclusion that consumers value nicotine for its pharmacological effects.

A more recent study cited by RJR attempted to quantify the sensory responses to cigarettes containing varying levels of nicotine.[354] This study did not even consider

---

[351] Thurauf N, Renner B, Kobal G, Responses recorded from the frog olfactory epithelium after stimulation with r(+) - and S(–) - nicotine, *Chemical Senses* 1995;20(3):337-344, at 342. *See* AR (Vol. 535 Ref. 96, vol. III.M).

[352] Baldinger B, Hasenfratz M, Battig K, Switching to ultralow nicotine cigarettes: effects of different tar yields and blocking of olfactory cues, *Pharmacology, Biochemistry and Behavior* 1995;50(2):233-239, at 238. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[353] Darkis FR, Baisden LA, Gross PM, Wolf FA, Flue-cured tobacco: chemical composition of rib and blade tissue, *Industrial and Engineering Chemistry* 1952;44(2):297-301, at 300-301. *See* AR (Vol. 519 Ref. 103, vol. II).

[354] Gordin HH, Perfetti TA, Mangan PP, A quantification of sensory responses related to dynamic cigarette performance variables, *Tobacco Science* 1987;31:23-27. *See* AR (Vol. 519 Ref. 103, vol. II).

whether any sensory responses to nicotine are important to smokers. The authors did not mention the number of subjects in the study. Nor did they account for the fact that cigarettes with varying nicotine levels also were different in many other ways; for example, they had different tip drafts, tipping porosities, plug wraps, and air dilution. Much of the data were not published with the study. FDA notes that this study—despite serious flaws—still found that tobacco taste was *not* associated with nicotine content.

A second recent study cited by RJR attempted to determine the smallest amount of nicotine change detectable to the user.[355] It did not address whether any nicotine change produces any important sensory effects. The authors concluded only that there is a detectable "perceptual response" to nicotine, which could be described as either throat harshness or "strength." The study did not distinguish between sensory and central pharmacological effects of nicotine.

The third recent study is an RJR presentation at a conference held in 1994, after FDA's investigation into nicotine was under way.[356] The presentation purported to show that nicotine's sensory effects are important in a consumer's acceptance of tobacco products, but the study failed to support this claim. Indeed, a principal author of the study conceded to FDA in 1994 that "we were not able to separate out the importance of the

[355] Gordin HH, Perfetti TA, Hawley RW, Nicotine just noticeable difference study of full flavor low "tar" and ultra low "tar" non-menthol 85mm products, *Tobacco Science* 1988;32:62-65. *See* AR (Vol. 519 Ref. 103, vol. II).

[356] Pritchard WS, Robinson JH, *The Sensory Role of Nicotine in Cigarette "Taste," Smoking Satisfaction and Desire to Smoke*, presented at the International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II, Montreal (Jul. 21-24, 1994). *See* AR (Vol. 519 Ref. 103, vol. II).

sensory aspects versus the pharmacological."[357] FDA notes that this study, despite serious flaws, still found that nicotine levels had *no* effect on smooth taste, harsh taste, or aftertaste of cigarettes.

Thus, the industry has presented no data that show that nicotine's flavor or sensory effects are important to consumer acceptance. Even if the industry had produced evidence to support its position, however, nicotine's pharmacological effects would still explain virtually all consumer use. As described in section II.B.3., below, the sensory aspects of tobacco consumption are important to consumers only in how they are linked to the pharmacological effects of nicotine.

Compared with the hundreds of studies conducted around the world demonstrating the pharmacological significance of nicotine to tobacco consumers—a conclusion that reflects universal scientific agreement—the evidence to support the assertion that nicotine's sensory role is important to consumers is unconvincing. Thus, the industry has provided no basis to conclude that nicotine's role in tobacco use is to provide taste, flavor, or any other nonpharmacological sensation.

3. Other Factors Associated with Tobacco Use Are Secondary to Pharmacological Effects

FDA has established above that consumers use tobacco products for the pharmacological effects of nicotine. The tobacco industry argues that consumers use tobacco for a variety of nonpharmacological purposes, including for taste, out of habit and ritual, and for social reasons. The Agency recognizes that there are many effects of

[357] Robinson J, Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 228. *See* AR (Vol. 255 Ref. 3445).

tobacco use perceived by some consumers as nonpharmacological in nature. In surveys, for example, some tobacco users say they like the taste of the product; others report enjoying the ritual involved in its consumption. The evidence before the Agency demonstrates, however, that the nonpharmacological factors associated with tobacco consumption are secondary to the pharmacological reasons for consumer use of tobacco. Indeed, FDA concludes that consumers use tobacco products "nearly exclusively" for the pharmacological effects of nicotine.

This conclusion is supported by comments from the Coalition on Smoking OR Health, representing the American Heart Association, American Lung Association, and American Cancer Society. The Coalition explains:

> The physicians and health professionals who comprise our organizations provide the health care for virtually all tobacco users in the United States. Based upon our long term experience as well as our review of the scientific literature, it is our conclusion that the *vast majority of people who use nicotine containing cigarettes and smokeless tobacco products do so to satisfy their craving for the pharmacological effects of nicotine*; that is, to satisfy their drug dependence or addiction. While the published scientific literature on the point is conclusive in our scientific opinion, there may be no better evidence of the reason people use these products than the accumulative, daily experience of the health care professionals who are our members.[358]

One basis for FDA's finding of nearly exclusive tobacco use for nicotine's pharmacological effects is that tobacco products do not exist commercially without nicotine. If taste, for example, were an independent reason for use of tobacco products—as claimed by the industry—one would expect to find that very-low-nicotine products that

[358] Coalition on Smoking or Health, Comment (Jan. 2, 1996), at 6 (emphasis added). *See* AR (Vol. 533 Ref. 102).

preserve tobacco taste would be popular on the market. But there are no such products. The tobacco industry itself knows that a tobacco product without nicotine is not acceptable to consumers. For example, an attorney representing RJR stated that the company would never eliminate nicotine from its cigarette alternative, because "without nicotine, you don't have a cigarette."[359] A former Philip Morris researcher similarly stated that it was well-known within Philip Morris that nicotine delivery was more important than flavor in consumer acceptance of cigarettes. According to this researcher, it was believed within the company that while consumers might accept a cigarette that had adequate nicotine but marginal flavor, they were unlikely to accept a cigarette with relatively good flavor but "not enough" nicotine.[360]

A second basis for FDA's finding is that the details of tobacco use can be distinguished from the basic motivation for tobacco use. For example, researchers have demonstrated that consumers will pick a favorite cigarette brand among several that deliver adequate nicotine.[361] Habits may also explain specific patterns of cigarette consumption. For example, a smoker may enjoy smoking during his afternoon work break; another may like to smoke in the company of a particular friend. These factors commonly determine the details of use of many addictive substances, including opioids

[359] Memorandum of meeting between Hutt PB, representing RJR Nabisco Inc., and FDA representatives (Oct. 23, 1987). *See* AR (Vol. 34 Ref. 558).

[360] Declaration of Uydess IL (Feb. 29, 1996), at 11-14. Comments concerning this declaration are addressed in section II.C.6., below. *See* AR (Vol. 638 Ref. 1).

[361] Boren JJ, Stitzer ML, Henningfield JE, Preference among research cigarettes with varying nicotine yields, *Pharmacology, Biochemistry and Behavior* 1990;36(1):191-193. *See* AR (Vol. 535 Ref. 96, vol. III.A).

and alcohol.[362] But they are separate from the underlying reason for such use, the pharmacological effects of the drugs.

Third, FDA agrees with experts in the field of addiction medicine that nonpharmacological factors associated with tobacco use are important to consumers only because they have become inextricably linked to nicotine's pharmacological effects. Extensive research in the field of behavioral psychology has demonstrated how animals and people come to associate environmental stimuli (taste, rituals, etc.) with the pharmacological effects of addictive drugs. In the extreme form, providing the stimulus alone leads to the user experiencing the pharmacological effect of the drug. This is called a "conditioned response." Thus, a heroin user who says he likes the feel of the needle in his arm has linked the sensation with the pharmacological "high" that inevitably follows. This heroin addict may even report a "high" after the injection of saline.[363] But he or she still injects "nearly exclusively" for the pharmacological effects of heroin.

Similarly, evidence in animals and humans demonstrates that nonpharmacological factors such as taste and habit are important to tobacco consumers only because they have become inextricably linked to the effects of the addictive drug. As one prominent addiction specialist noted, "Animal experiments support the view that the sensory and

[362] Surgeon General's Report, 1988, at 15. *See* AR (Vol. 129 Ref. 1592).

[363] O'Brien CP, Testa T, Ternes J, Greenstein R, Conditioning Effects of Narcotics in Humans, in *Behavioral Tolerance: Research and Treatment Implications,* NIDA Research Monograph 18 (Washington DC: Government Printing Office No. 017-024-00899-8, Jan. 1978), at 67-71. *See* AR (Vol. 535 Ref. 96, vol. III.L).

olfactory stimuli associated with tobacco-using behavior function as conditioned stimuli due to their previous association with nicotine."[364]

Clinicians who treat patients dependent upon tobacco products have reached the same conclusion.[365] For example, some smokers identify the sensation of "tracheal scratch" associated with inhalation as pleasurable. But, as the American Society of Addiction Medicine (ASAM) comments:

> The tracheal 'scratch' which arises from the inhalation of cigarette smoke is a sensation which has become paired with the absorption of nicotine into the bloodstream and the consequent effects of nicotine on the brain. *People do not smoke for the 'scratch'; they smoke for the nicotine.* The "scratch" tells the smoker that nicotine is on its way to the brain and provides some indication of the relative dose which will shortly be coming.[366]

Other evidence of "conditioned responses" comes from studies of the early stages of tobacco withdrawal, when providing the environmental stimuli of smoking without nicotine (i.e., very-low-nicotine cigarettes) alleviates some of the abstinent smokers' discomfort.[367] This is analogous to heroin users feeling a psychological benefit from injecting saline when heroin is not available.[368] In both cases, the benefits of the

---

[364] Jaffe JH, Tobacco smoking and nicotine dependence, in *Nicotine Psychopharmacology* (Oxford: Oxford University Press, 1990), 1-29, at 14. *See* AR (Vol. 535 Ref. 96, vol. III.G).

[365] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[366] American Society of Addiction Medicine, Comment (Dec. 29, 1995), at 5 (emphasis added). *See* AR (Vol. 528 Ref. 97).

[367] Butschky MF, Bailey D, Henningfield JE, Pickworth WB, Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers, *Pharmacology, Biochemistry and Behavior* 1995;50(1):91-96. *See* AR (Vol. 442 Ref. 7484).

[368] O'Brien CP, Testa T, Ternes J, Greenstein R, Conditioning Effects of Narcotics in Humans, in *Behavioral Tolerance: Research and Treatment Implications,* NIDA Research Monograph 18 (Washington DC: Government Printing Office No. 017-024-00899-8, Jan. 1978), at 67-71. *See* AR (Vol. 535 Ref. 96, vol. III.L).

nonpharmacological stimuli rapidly decrease as the stimuli are no longer associated with the drug's effects.[369]

ASAM concluded: "People who use tobacco products build up rituals around nicotine ingestion and experience sensations in the process of using tobacco that become valuable to them. However, *these rituals would not exist, and the sensations would be of no value, but for the associated delivery of nicotine to the brain.*"[370] Thus, when someone says he or she smokes for the "taste" or "feel" or "ritual" of cigarette consumption, these "reasons for use" are inextricably tied to the pharmacological effects of nicotine.[371]

Accordingly, FDA concludes that consumers use tobacco products "predominantly" and "nearly exclusively" for one or more of the pharmacological effects of nicotine.

4. Responses to Additional Comments

a. General Comments on Consumer Use

1. The American Society of Addiction Medicine (ASAM) argues that the common practice of inhaling cigarette smoke demonstrates that consumers use cigarettes for the pharmacological effects of nicotine. According to ASAM, because of the relatively

---

[369] *Id.*

Butschky MF, Bailey D, Henningfield JE, Pickworth WB, Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers, *Pharmacology, Biochemistry and Behavior* 1995;50(1):91-96. *See* AR (Vol. 442 Ref. 7484).

[370] American Society of Addiction Medicine, Comment (Dec. 29, 1995), at 14 (emphasis added). *See* AR (Vol. 528 Ref. 97).

[371] Surgeon General's Report, 1988, at 58-59. *See* AR (Vol. 129 Ref. 1592).